Quetiapine and Clarithromycin–Induced Neuroleptic Malignant Syndrome

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Abstract: We report a case of neuroleptic malignant syndrome possibly caused by the combined administration of quetiapine and clarithromycin in a 75-year-old male patient. He was receiving quetiapine regularly. Two days before his admission to the hospital, he had been feverish and started receiving clarithromycin without consulting a doctor. Clarithromycin administration was interrupted 3 days after his admission because it was ineffective and because his clinical state was deteriorating. The patient presented altered level of consciousness and excessive muscular rigidity on his limbs, while he remained feverish (38.7 °C). Laboratory abnormalities included elevated serum creatine phosphokinase level (5.387 U/L), leukocytosis, and low serum iron. The patient was diagnosed with neuroleptic malignant syndrome, and quetiapine was immediately discontinued. After the following days, his muscle rigidity and mental status ameliorated, his fever withdrew, and his laboratory findings improved. The various features of the case are discussed in view of the fact that the concomitant administration of cytochrome 3A4 inhibitors, such as clarithromycin, is suggested to cause an increase of plasma concentrations of quetiapine. Thus, physicians should have a high index of suspicion of the interactions of commonly administered medications.

Key Words: neuroleptic malignant syndrome, atypical antipsychotics, quetiapine, clarithromycin, rhabdomyolysis

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Neuroleptic malignant syndrome (NMS) is a rare, severe, and potentially fatal adverse reaction usually seen in the context of treatment with high-potency typical neuroleptic agents. However, in the recent years, several cases of the syndrome have been reported with the use of the newer atypical antipsychotics, including quetiapine.[1]

The incidence of NMS is uncertain. It probably occurs in less than 1% of patients treated with typical antipsychotics[2] and seems to be rarer in atypical antipsychotics.

The exact pathogenesis has not been clarified yet, although dopamine receptor blockade and central noradrenergic hyperactivity have a dominant position in current suggested theories.[3]

The manifestations of the syndrome include hyperthermia, muscle rigidity, autonomic instability (tachycardia, diaphoresis), disturbances in conscious state, catatonia, as well as increased creatine phosphokinase (CPK) level, neutrophile leukocytosis, and low serum iron.

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In the following, we report a case of a patient diagnosed with NMS who has been induced by the coadmittance of quetiapine and clarithromycin during his hospitalization.

A 75-year-old male patient admitted from the emergency department to the internal medicine department of the Attikon University General Hospital with fever and astasia-abasia. Two days before his admission, he had been feverish (37.8 °C) and started receiving medication with 1000-mg/d clarithromycin by his carers without any medical prescription. At the same time, he continued receiving regular medication with quetiapine IR (125 mg/d) for insomnia and behavioral problems.

At his admission, the laboratory findings included mildly elevated CPK level (390 U/L) and other nonspecific findings. Clarithromycin administration continued in the hospital in the same dosage (500 mg every 12 hours) for 3 more days. Then, it was interrupted, first, because it was ineffective and, second, because of deterioration of his clinical state. Under these circumstances, he was examined by the liaison psychiatrists with a question concerning his psychiatric medication. By the time of the first psychiatric evaluation (3 days after his admission), the patient was stuporous with excessive muscular rigidity on his limbs (lead pipe rigidity/dead cockroach position) and feverous with temperatures ranging up to 38.7 °C with a profuse diaphoresis. His heart rate was labile with high blood pressures (180-110 mm Hg). The laboratory abnormalities have been deteriorated, including elevated serum CPK level (5.387 U/L), leukocytosis (white blood cell count, 12.450 per μL), mild elevation of liver transaminases (aspartate aminotransferase, 80 U/L; alanine aminotransferase, 49 U/L) and γ-glutamyl transpeptidase (79 U/L), as well as mild electrolytic abnormalities (Ca, 8.3 mg/dL; Na, 149 mEq/L). The serum iron concentration was found at the lowest reference range (Fe, 39 μg/dL).

The patient was diagnosed with NMS, the neuroleptic (quetiapine) was immediately discontinued, and supportive care under close medical attention was intensified. After the following days, rigidity progressively ameliorated, and gradually, 2 days later, his mental status improved and his fever withdrew. The general condition and laboratory findings improvement continued (CPK, 249 U/L; white blood cell count, 9.800 per μL; Na, 140 mEq/L), and the following week, the hospitalization ended. During a follow-up examination 1 month later, the rigidness had totally withdrawn.

DISCUSSION

We would like to describe a case of NMS probably caused by the rise of quetiapine serum levels after an accidental coadministration of clarithromycin. To the best of our knowledge, there is no such case previously reported.

Concerning the role of quetiapine in NMS, there are several cases of NMS[1] or rhabdomyolysis[4] associated with quetiapine medication reported in the literature. However, it seems that, very rarely, quetiapine per se induces NMS. In most of the cases reported, the NMS is induced either after a coadministration of quetiapine with other medication or when other medical conditions have been involved.[5]

The central role in our differential diagnosis is the fact that cytochrome (CYP) P450 3A4 is the primary enzyme responsible for the CYP450-mediated metabolism of quetiapine. The concomitant administration of CYP3A4 inhibitors, such as clarithromycin, is suggested to cause an increase of plasma concentrations of quetiapine. In vivo assessments, which were carried out by the pharmaceutical company, have indicated that coadministration of quetiapine (dosage of 25 mg) and a potent CYP3A4 inhibitor, such as ketoconazole, leads to a 84% decrease in oral clearance (ie, the rate of clearance of drugs administered orally), resulting in a 6.2-fold increase in the area under the curve of quetiapine. Moreover, there is evidence of increase of quetiapine plasma concentrations and its metabolites upon concomitant administration of erythromycin[6]; clarithromycin has also been suggested to inhibit quetiapine metabolism, leading to increased plasma concentration of quetiapine.[7] A case of NMS is reported to be induced by quetiapine upon coadministration of fluvoxamine.[8] In addition, a case of possible NMS upon coadministration of quetiapine, clarithromycin, and simvastatin has been reported. However, in this case, the etiologic relation between NMS and quetiapine-clarithromycin metabolic interaction has not been demonstrated because of the presence of simvastatin, which is also metabolized by the CYP450 3A4 enzyme.[9]

Furthermore, consideration should be given to dose modifications of neuroleptics (antipsychotics) in elderly patients because of lower oral clearance and the consequent increase of metabolites plasma concentration. Reduced oral clearance in the elderly has been found for quetiapine.[10] In particular, the oral clearance of quetiapine was reduced 30% to 50% in elderly patients (65 years or older) when compared with younger patients, indicating that dosing adjustment in elderly patients is necessary.[11] Clinical experience with quetiapine in patients with renal impairments is limited. Consequently, in the present case, the age of the patient plays an aggravating role in increasing plasma concentrations of quetiapine and in reducing the threshold for adverse effects.

Regarding the differential diagnosis, the possibility of quetiapine-induced rhabdomyolysis should be excluded because there were special clinical and laboratory findings suggesting NMS. Apart from this, there was no recent change in the quetiapine dosage. Moreover, catatonia caused by general medical condition (infection) that underwent to malignant catatonia, a situation hard to differentiate from NMS, does not seem possible because these cases are extremely rare and normally have precedent catatonic signs (psychomotor disturbance, such as motor immobility or excessive motor activity, peculiarities of voluntary movements). Finally, the possibility of a feverous infection that reduced the threshold for NMS at the same time with the coadministration of clarithromycin-quetiapine is more appealing than the possibility that NMS was destined to evolve in this patient exclusively because of ever, independent of clarithromycin administration. The simultaneous initiation of rhabdomyolysis and other clinical and laboratory findings with the clarithromycin administration, as well as the excellent clinical improvement of the patient after quetiapine administration was stopped, strongly indicate this possibility.

The management of the case presented in this report included the immediate discontinuation of the suspected causative agent (quetiapine) and intensive supportive care with close monitoring of clinical signs and laboratory values. In the literature, there is no general consensus on specific pharmacological treatments (ie, dantrolene, bromocriptine, amantadine) and there is only limited evidence on whether specific remedies can facilitate recovery and improve outcome. In addition, the use of these medications is associated with serious adverse effects.

SUMMARY

- Although potent neuroleptics are more often related with NMS, all antipsychotic agents, typical or atypical, may precipitate the syndrome.
- In the present case, the coadministration of a frequently used antibiotic and an atypical neuroleptic agent is supposed to be the etiologic factor for NMS. Thus, the findings of the case reported suggest that physicians should have a high index of suspicion of the interactions and the adverse effects caused by the concomitant administration of commonly administered medications (especially in the elderly patients).
- Finally, this report demonstrates the fact that prevention, early recognition, and early intervention are essential to prevent the grave outcome and potential fatality of NMS.

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